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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 471/04, A61K 31/505 | A1

(11) International Publication Number: **WO 98/45293**

(43) International Publication Date: 15 October 1998 (15.10.98)

(21) International Application Number: PCT/EP98/02139

(22) International Filing Date: 3 April 1998 (03.04.98)

(30) Priority Data:
9707251.6 10 April 1997 (10.04.97) GB

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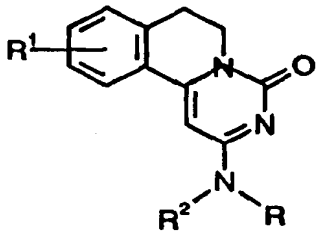
(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PYRIMIDO–ISOQUINOLINE COMPOUNDS WITH ANTICONVULSIVE ACTION

(57) Abstract

A method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti–convulsive agents, such as epilepsy including post–traumatic epilepsy, Parkinson's disease, psychosis, migraine,



(I)

cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia and narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and amyotrophic lateral sclerosis (ALS) comprises administering to the sufferer in need thereof an effective or prophylatic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof; in which R^1 is hydrogen or up to three substituents independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl and hydroxy C_{1-6}alkyl, or two R^1 groups form a methylenedioxy; R^2 is hydrogen or C_{1-6}alkyl, and R is R^3 or R^3CO where R^3 is C_{3-7}cycloalkyl, phenyl or phenyl C_{1-6}alkyl in which the cyclic moieties are optionally substituted by up to three substituents independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylcarbonyl, hydroxy C_{1-6}alkyl and phenylcarbonyloxy C_{1-6}alkyl.

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PYRIMIDO-ISOQUINOLINE COMPOUNDS WITH ANTICONVULSIVE ACTION

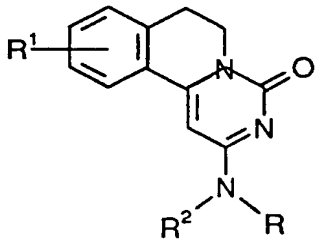
This invention relates to a novel method of treatment and to novel compounds for use in that method.

US Patent 4482556 (Lal et al) and J.Med Chem 1984, 27, 1470 disclose a group of pyrimido(6,1-a)isoquinolin-4-one derivatives, said to be useful as hypotensive agents, bronchodilators and anti-allergenics.

It has now been surprisingly found that pyrimidoisoquinolinone derivatives of formula (I) below possess anti-convulsant activity and are therefore believed to be useful in the treatment and/or prevention of anxiety, mania, depression, panic disorders and/or aggresssion, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and amyotrophic lateral sclerosis (ALS).

Accordingly the present invention provides a method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggresssion, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, MS and motor

neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction or amyotrophic lateral sclerosis (ALS); comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

in which R^1 is hydrogen or up to three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl and hydroxy C_{1-6} alkyl, or two R^1 groups form a methylenedioxy,
R^2 is hydrogen or C_{1-6} alkyl, and
R is R^3 or R^3CO where
R^3 is C_{3-7} cycloalkyl, phenyl or phenyl C_{1-6} alkyl in which the cyclic moieties are optionally substituted by up to three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, hydroxy C_{1-6} alkyl and phenylcarbonyloxy C_{1-6} alkyl.

Suitable halo substituents include fluoro, chloro, iodo and bromo. Alkyl groups alone or as part of another group are typically methyl, ethyl, *n*- or *iso*-propyl, or *n*-, *iso*- or *t*-butyl. Cycloalkyl groups are typically cyclopentyl, cyclohexyl or cycloheptyl.

A suitable group of compounds of formula (I) have
R^1 as hydrogen or methoxy,
R^2 as hydrogen or methyl
R^3 as cyclopentyl, phenyl, benzyl or phenyl substituted by one or two chloro, iodo, methyl, methoxy, *iso*-propyl,acetyl, hydroxymethyl or phenylcarbonyloxymethyl groups.

Examples of suitable compounds of formula (I) are:

9,10-dimethoxy-2-(3,5-dichlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(2-methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(3-chlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-iodophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-*iso*-propylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2,4-dimethoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(N-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(cyclopentylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(benzylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(phenylamino)-6,7-dihydro-4*H*-pyrimido[6, 1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-acetylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(benzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-hydroxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(3-chlorobenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-methoxybenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-phenylcarbonyloxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
2-(phenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a] isoquinolin-4-one
2-(2-methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

When synthesised, these compounds may be in salt form, and such salts also form part of this invention. Such salts may be used in preparing pharmaceutically acceptable salts. The compounds and their salts may be obtained as solvates, such as hydrates, and these also form part of this invention.

The use of above-listed compounds and pharmaceutically acceptable salts thereof, especially the hydrochloride, and pharmaceutically acceptable solvates, especially hydrates, forms a preferred aspect of the present invention.

The administration of such compounds to a mammal may be by way of oral, parenteral, sub-lingual, nasal, rectal, topical, or transdermal administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of the mammal. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 400 mg such as 2, 5, 10, 20, 30, 40, 50, 100, 200, 300 and 400 mg of the active compound. Unit doses will normally be administered once or more than once per day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 4 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 1 to 1000 mg, for example 1 to 500 mg, that is in the range of approximately 0.01 to 15 mg/kg/day, more usually 0.1 to 6 mg/kg/day, for example 1 to 6 mg/kg/day.

It is greatly preferred that the compound of formula (I) is administered in the form of a unit-dose composition, such as a unit dose oral, including sub-lingual, nasal, rectal, topical, transdermal or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as

sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

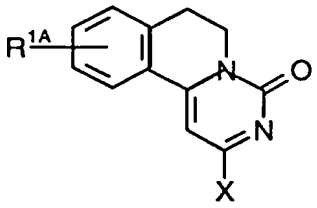
Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

Accordingly, in a further aspect, the present invention provides a pharmaceutical composition for use in the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggresssion, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and/or amyotrophic lateral sclerosis (ALS); which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

In a further aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggresssion, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and/or amyotrophic lateral sclerosis (ALS).

Compounds of formula (I) used in this invention may be prepared by reacting a compound of formula (II)



(II)

where R^{1A} is respectively R^1 as defined for formula (I) or a group convertible to R^1 with either

(a) a compound of formula $R^{3A}NR^{2A}H$, in which case X in formula (II) is a halogen (for compounds of formula (I) in which R is R^3), or

(b) a compound of formula $R^{3A}COY$ where Y is a halogen, in which case X in formula (II) is $NR^{2A}H$ (for compounds of formula (I) in which R is R^3CO),

where R^{2A} and R^{3A} are respectively R^2 and R^3 as defined for formula (I) or a group convertible to R^2 and R^3,

and where required converting an R^{1A}, R^{2A} or R^{3A} group to an R^1, R^2 or R^3 group, converting one R^1, R^2 or R^3 group to another R^1, R^2 or R^3 group, converting a salt product to the free base or another pharmaceutically acceptable salt, or converting a free base product to a pharmaceutically acceptable salt.

Conversions of an R^A or R^{1A} group to a R or R^1 group typically arise when a protecting group is needed during the above coupling reaction or during the preparation of the reactants by the procedures described below. Interconversion of one R or R^1 group to another typically arises when one compound of formula (I) is used as the immediate precursor of another compound of formula (I), or when it is easier to introduce a more complex or reactive substituent at the end of a synthetic sequence.

Reaction (a) is typically carried out by heating the reactants together, preferably under reflux in a suitable inert solvent, such as chloroform optionally in the presence of a tertiary amine base such as 2,6-lutidine. Further details of procedures for the preparation of compounds in which for use in this invention can be found in US 4482556 cited above and by study of the Examples below.

Reaction (b) may be carried out under conventional conditions for condensing amines with acid chlorides, in the present case typically by mixing the reactants together at room

temperature in a suitable inert solvent, such as chloroform optionally in the presence of a suitable tertiary amine base or catalyst such as N,N-dimethylamino-pyridine.

Compounds of formula $R^{3A}NR^{2A}H$ are commercially available or can be prepared by conventional substitution of commercially available aniline or cycloalkylamine derivatives and by analogy with the procedures set out in US 4482556.

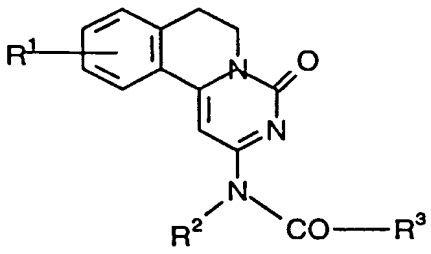
Compounds of formula $R^{3A}COY$ are commercially available or can be prepared by further substitution of commercially available benzoic acid derivatives compounds using conventional procedures.

Compounds of formula (II) in which X is a halogen may be prepared by procedures set out in US 4482556, J.Med.Chem., 1984, 27, 1470 and in the Descriptions below. In general terms the preparation can commence with an appropriately substituted phenylethylamine, which is commercially available or can be prepared by conventional substitution of phenylethylamine or a commercially available derivative thereof. The amine may be converted to the corresponding phenylethylurea by treating the amine with potassium cyanate under acid conditions. The urea may be converted to an N-substituted barbituric acid by adding the urea to a mixture of sodium ethoxide and diethyl malonate in a suitable solvent, such as ethanol. The resultant barbituric acid may be heated with phosphorus oxychloride to obtain a compound of formula (II) in which X is chlorine. Other halogen derivatives can be prepared by analogous procedures.

As an alternative, a compound of formula (II) in which X is chlorine (which is a 6,7-dihydro-pyrimido-isoquinolin-4-one) may be prepared by reaction of phosphorus oxychloride with the corresponding 2,4-dione using a method similar to that of G.A.Howarth, Heterocycles, 1989, 29, 1929. The dione may be prepared by heating an appropriately substituted N-phenylethyl cyanoacetamide in polyphosphoric acid.

Compounds of formula (II) in which X is $NR^{2A}H$ may be prepared by making the compound of formula (II) in which X is halogen as described above, and heating it with liquid ammonia or the amine $R^{3A}NR^{2A}H$ under pressure.

Among the compounds proposed for use in the method of treatment of this invention, the following compounds of formula (Ia) are believed to be novel, and form a further aspect of this invention:



(Ia)

in which R^1 is hydrogen or up to three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl and hydroxy C_{1-6} alkyl,
R^2 is hydrogen or C_{1-6} alkyl, and
R^3 is C_{3-7} cycloalkyl, phenyl or phenyl C_{1-6} alkyl in which the cyclic moieties are optionally substituted by up to three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, hydroxy C_{1-6} alkyl and phenylcarbonyloxy C_{1-6} alkyl.

Examples of compounds of formula (Ia) are:

Example 17
9,10-dimethoxy-2-(benzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 18
9,10-dimethoxy-2-(3-chlorobenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 19
9,10-dimethoxy-2-(2-methoxybenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

A further aspect of this invention is the preparation of the above novel compounds by the reaction of a compound of formula (II) with a compound of formula $R^{3A}COY$, as described above.

Where intermediates in that process are novel, they also form part of this invention

Also the following individual compounds of formula (I) are believed to be novel, and are also part of this invention:

Example 1
9,10-dimethoxy-2-(3,5-dichlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 2
9,10-dimethoxy-2-(2-methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 3
9,10-dimethoxy-2-(2-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 4
9,10-dimethoxy-2-(3-chlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 5
9,10-dimethoxy-2-(2-iodophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 6
9,10-dimethoxy-2-(2-*iso*-propylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 8
9,10-dimethoxy-2-(N-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 9
9,10-dimethoxy-2-(cyclopentylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 10
9,10-Dimethoxy-2-(benzylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 12

9,10-dimethoxy-2-(2-acetylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 13

9,10-dimethoxy-2-(2-hydroxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 14

9,10-dimethoxy-2-(2-phenylcarbonyloxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

Example 15

2-(phenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a] isoquinolin-4-one

Example 16

2-(2-methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

In a further aspect the invention provides a pharmaceutical composition comprising any novel compound of this invention, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier; and also the use of any novel compound of this invention, or a pharmaceutically acceptable salt or solvate thereof, as a therapeutic agent, in particular for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and amyotrophic lateral sclerosis (ALS).

The preparation of compounds used in this invention and novel compounds of this invention is further illustrated by the following Descriptions and Examples. The utility of

the compounds in the method of treatment of this invention is shown by the Pharmacological Data that follow the Examples.

Description 1

N-2-(3,4-Dimethoxyphenyl)ethyl urea

The procedure was similar to that described by F. Kienzle *et al.*, Helv. Chim., Acta. 1986, 69, 1671.

To a mixture of 3,4-dimethoxyphenylethylamine (6.1g; 34mmol) in water (35ml) was added 5M HCl (6.73ml). The resultant orange solution was heated to 50°C and treated with portionwise addition of potassium cyanate (2.73g; 34mmol) over 1.5h. Heating was continued for a further 2h and then the mixture was cooled to 0°C. The resultant precipitate was removed by filtration, washed well with ice-cold water and drying *in vacuo* gave a white solid (6.1g, 81%).

Description 2

N-2-(3,4-Dimethoxyphenyl)ethyl barbituric acid

A solution of sodium ethoxide in ethanol (made from sodium 0.74g in dry ethanol 16ml) was treated with diethyl malonate (5.2g, 4.9ml) in ethanol (50ml) at reflux, followed by dropwise addition of the urea D1 (5.97g, 26.7mmol) in dry ethanol (66ml). The mixture was heated under reflux for 20 h and then allowed to cool. The mixture was cooled to 0°C, treated with 5% HCl (30ml), water (300ml) and the resultant precipitate removed by filtration. The residue was dried *in vacuo* at 50°C to give the title compound as an off white powder (5.31g; 69%).

Description 3

2-Chloro-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido-[6,1-a]isoquinolin-4-one

A mixture of D2 (5.29g, 18.1mmol) and phosphorus oxychloride (100ml) was heated under reflux for 18h and then allowed to cool (as outlined by B.Lal *et al.*, J. Med. Chem., 1984, 27, 1470). The mixture was poured onto ice/water (60ml) and the pH adjusted to 11 with 40% NaOH. Extraction with ethyl acetate followed by work-up and trituration of the product with ether gave the title compound as an orange powder (3.3g; 62%).

^{1}H NMR (250MHz, $CDCl_3$) δ: 3.00 (2H, t), 3.98 (2x3H, s), 4.23 (2H, t), 6.65 (1H, s), 6.78 (1H, s), 7.12 (1H, s).

Description 4

2-Amino-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6, 1-a]isoquinolin-4-one

2-Chloro-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6, 1-a]isoquinolin-4-one (6.0g) and liquid ammonia (150 ml) were heated at 85 C for 4h in a pressure bomb. The vessel was allowed to cool and evaporation of the liquid afforded the title compound (5.7g) which was used without further purification.

m/z(API+): 274 (MH^+; 90%).

Description 5

6,7-Dihydro-4*H*-pyrimido[6,1-a]isoquinolin-2,4-dione

N-Phenylethyl cyanoacetamide (0.5g) in polyphosphoric acid (20g) was heated at 110°C for 20h [as outlined in Hoechst patent US 4482556 (1984)]. The mixture was poured into water and then extracted with chloroform. The aqueous layer was neutralised with 40% NaOH, with ice cooling, and the product extracted into dichloromethane. The material (260mg) from the organic layer was dissolved in ethanol (5ml) and added to a freshly prepared solution of ethanolic sodium ethoxide (73mg of sodium in ethanol 30ml). The mixture was stirred for 30 min and diethyl carbonate (2ml) was added. The mixture was heated under reflux for 6h and then ice was added and the pH adjusted to 7 with 5N HCl. The resultant white precipitate was removed by filtration and dried (0.19g).

$m/_z$ (API+):215 (MH^+; 100%).

Description 6

2-Chloro-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

A mixture of the dione **D5** (5.24g) and phosphorus oxychloride (50ml) was treated according to the method of Description 3. Flash chromatography of the crude product on silica using 10% methanol:dichloromethane gave the title compound (3.0g).

Example 1

9,10-Dimethoxy-2-(3,5-dichlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

A solution of 2-chloro-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one (400mg, 1.36mmol) in 2,6-lutidine (100ml) was treated with 3,5-dichloroaniline (222mg) in chloroform (3ml) and the mixture heated under reflux for 20h. Evaporation *in vacuo* gave a residue which was purified by flash chromatography on silica using 2-10% methanol:dichloromethane. Combination of appropriate fractions gave the title compound as a cream solid (441mg; 77%), m.p. 305-7°C

$m/_z$ (API+):418 (MH^+; 100%).

Example 2

9,10-Dimethoxy-2-(2-methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

A solution of 2-chloro-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one (514mg, 1.76mmol) and 2-methoxyaniline (550mg; 5.28mmol) in chloroform (5ml) was heated under reflux overnight. The mixture was diluted with dichloromethane, washed with 10% sodium hydroxide, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was triturated with ether to give a pale yellow solid which was recrystallised from chloroform-ethyl acetate to give the title compound (514mg, 77%), m.p. 274-5°C

^1H NMR (400MHz, DMSO-d^6)δ: 2.93 (2H, t, CH_2), 3.86 (3H, s), 3.87 (3H, s), 3.90 (3H, s), 3.98 (2H, t, NCH_2), 6.79 (1H, s, H-10), 6.96 (1H, m), 7.07 (2H, m), 7.25 (1H, s, H-9), 8.36 (1H, d), 8.60 (1H, s, NH); m/z(API+): 380 (MH^+; 100%)

In the following Examples 3-16, compounds were made using methods similar to those described above for Examples 1 and 2.

Example 3

9,10-Dimethoxy-2-(2-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m.p. 255°C

Example 4

9,10-Dimethoxy-2-(3-chlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m.p. 295°C

Example 5

9,10-Dimethoxy-2-(2-iodophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m.p. 252°C

Example 6

9,10-Dimethoxy-2-(2-isopropylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m.p. 259°C.

Example 7

9,10-Dimethoxy-2-(2,4-dimethoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m.p. 239°C

Example 8

9,10-Dimethoxy-2-(N-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

This was prepared from Description 4 and N-methyl-aniline using a procedure similar to that employed for Example 2.

Example 9

9,10-Dimethoxy-2-(cyclopentylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m.p. 260°C

Example 10

9,10-Dimethoxy-2-(benzylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m.p. 207°C

Example 11

9,10-Dimethoxy-2-(phenylamino)-6,7-dihydro-4*H*-pyrimido[6, 1-a]isoquinolin-4-one

m.p. >300°C

Example 12

9,10-Dimethoxy-2-(2-acetylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m.p. 214-6°C

Example 13

9,10-Dimethoxy-2-(2-hydroxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m.p. 145-8°C

Example 14

9,10-Dimethoxy-2-(2-phenylcarbonyloxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

The title compound was prepared from Example 13 using the method of Example 17.

m/z(API+): 484 (MH^+, 3%), 362 ($MH^+ - PhCO_2$, 100%).

Example 15

2-(Phenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a] isoquinolin-4-one

m.p. 314°C

Example 16

2-(2-Methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

$m/_z$ (API+): 304 (MH^+; 100%).

Example 17

9,10-Dimethoxy-2-(benzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

2-Amino-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6, 1-a]isoquinolin-4-one (104mg, 0.38mmol) and DMAP (20 mg) in chloroform (15 ml) were treated with a solution of benzoyl chloride (60 mg, 0.40mmol). After 10 min at room temperature, the pale yellow solution was evaporated *in vacuo*. Chromatography on Kieselgel 60 in 1% methanol-dichloromethane afforded the title compound (114 mg, 80%). m.p. 213-215°C

m/z(API+): 378 (MH^+, 100%).

In the following Examples 18 and 19, compounds were made using procedures similar to that of Example 17.

Example 18

9,10-Dimethoxy-2-(3-chlorobenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m/z(API+): 412 (MH^+, 100%)

Example 19

9,10-Dimethoxy-2-(2-methoxybenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

m/z(API+): 408 (MH^+, 100%)

PHARMACOLOGICAL DATA

1. **Binding Assay Method**

WO 92/22293 (SmithKline Beecham) discloses compounds having anti-convulsant activity, including *inter alia* the compound *trans*-(+)-6-acetyl-4S-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol (hereinafter referred to as Compound

A). It has been found that the compounds of WO 92/22293 bind to a novel receptor obtainable from rat forebrain tissue, as described in WO 96/18650 (SmithKline Beecham). The affinity of test compounds to the novel receptor site is assessed as follows.

Method

Whole forebrain tissue is obtained from rats. The tissue is first homogenised in buffer (usually 50mM Tris/HCl, pH 7.4). The homogenised tissue is washed by centrifugation and resuspension in the same buffer, then stored at -70°C until used.

To carry out the radioligand binding assay, aliquots of tissue prepared as above (usually at a concentration of 1-2mg protein/ml) are mixed with aliquots of [3H]-Compound A dissolved in buffer. The final concentration of [3H]-Compound A in the mixture is usually 20nM. The mixture is incubated at room temperature for 1 hour. [3H]-Compound A bound to the tissue is then separated from unbound [3H]-Compound A by filtration through Whatman GF/B glass fibre filters. The filters are then washed rapidly with ice-cold buffer. The amount of radioactivity bound to the tissue trapped on the filters is measured by addition of liquid scintillation cocktail to the filters followed by counting in a liquid scintillation counter.

In order to determine the amount of "specific" binding of [3H]-Compound A, parallel assays are carried out as above in which [3H]-Compound A and tissue are incubated together in the presence of unlabelled Compound A (usually 3 μM). The amount of binding of [3H]-Compound A remaining in the presence of this unlabelled compound is defined as "non-specific" binding. This amount is subtracted from the total amount of [3H]-Compound A binding (i.e. that present in the absence of unlabelled compound) to obtain the amount of "specific" binding of [3H]-Compound A to the novel site.

The affinity of the binding of test compounds to the novel site can be estimated by incubating together [3H]-Compound A and tissue in the presence of a range of concentrations of the compound to be tested. The decrease in the level of specific [3H]-Compound A binding as a result of competition by increasing concentrations of the compound under test is plotted graphically, and non-linear regression analysis of the resultant curve is used to provide an estimate of compound affinity in terms of pKi value.

Results

Compounds of Formula (I) were active in this test. For example, the compounds of Examples 2, 3 and 6 gave pKi values greater than 7.

2. **MEST Test**

The maximal electroshock seizure (MEST) threshold test in rodents is particularly sensitive for detecting potential anticonvulsant properties[1]. In this model, anticonvulsant agents elevate the threshold to electrically-induced seizures whilst proconvulsants lower the seizure threshold.

Method

Mice (naive male, Charles River, U.K. CD-1 strain, 25 - 30g) are randomly assigned to groups of 10 - 20 and dosed orally or intraperitoneally at a dose volume of 10 ml/kg with various doses of compound (0.3 - 300 mg/kg) or vehicle. Mice are then subjected at 30 or 60 min post dose to a single electroshock (0.1 sec, 50Hz, sine wave form) administered via corneal electrodes. The mean current and standard error required to induce a tonic seizure in 50% (CC_{50}) of the mice in a particular treatment group is determined by the 'up and down' method of Dixon and Mood (1948)[2]. Statistical comparisons between vehicle- and drug-treated groups are made using the method of Litchfield and Wilcoxon (1949)[3].

In control animals the CC_{50} is usually 14 - 18 mA. Hence the first animal in the control group is subjected to a current of 16 mA. If a tonic seizure does not ensue, the current is increased for a subsequent mouse. If a tonic convulsion does occur, then the current is decreased, and so on until all the animals in the group have been tested.

The percentage increase or decrease in CC_{50} for each group compared to the control is calculated.

Studies are carried out using a Hugo Sachs Electronik Constant Current Shock Generator with totally variable control of shock level from 0 to 300 mA and steps of 2 mA are usually used.

Drugs are suspended in 1% methyl cellulose.

References

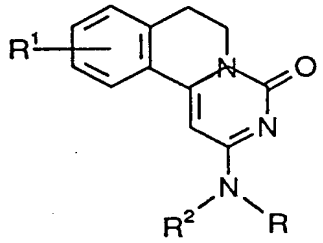
1. Loscher, W. and Schmidt, D. (1988). Epilepsy Res., **2**, 145-181
2. Dixon, W.J. and Mood, A.M. (1948). J. Amer. Stat. Assn., **43**, 109-126
3. Litchfield, J.T. and Wilcoxon, F.(1949). J. Pharmacol. exp. Ther., **96**, 99-113

Results

Compounds of formula (I) dosed by the oral route as a suspension in methyl cellulose and tested one hour post dosing showed an increase in seizure threshold.

Claims

1. A method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggresssion, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and amyotrophic lateral sclerosis (ALS) comprising administering to the sufferer in need thereof an effective or prophylactic amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

in which R^1 is hydrogen or up to three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl and hydroxy C_{1-6} alkyl, or two R^1 groups form a methylenedioxy,
R^2 is hydrogen or C_{1-6} alkyl, and
R is R^3 or R^3CO where
R^3 is C_{3-7} cycloalkyl, phenyl or phenyl C_{1-6} alkyl in which the cyclic moieties are optionally substituted by up to three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, hydroxy C_{1-6} alkyl and phenylcarbonyloxy C_{1-6} alkyl.

2. A pharmaceutical composition for use in the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggresssion, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and amyotrophic lateral sclerosis (ALS) which comprises a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

3. Use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggresssion, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, MS and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and amyotrophic lateral sclerosis (ALS).

4. A method according to claim 1, pharmaceutical composition according to claim 2, or use according to claim 3, wherein the compound of formula (I) is selected from the group consisting of:

9,10-dimethoxy-2-(3,5-dichlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(2-methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(2-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(3-chlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(2-iodophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(2-*iso*-propylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(2,4-dimethoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(N-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(cyclopentylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(benzylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(phenylamino)-6,7-dihydro-4*H*-pyrimido[6, 1-a]isoquinolin-4-one

9,10-dimethoxy-2-(2-acetylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(benzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(2-hydroxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(3-chlorobenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

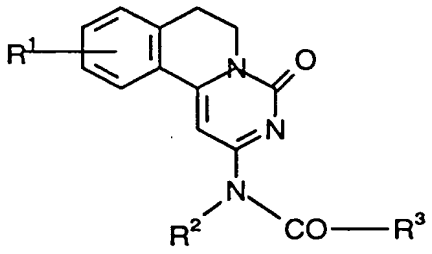
9,10-dimethoxy-2-(2-methoxybenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(2-phenylcarbonyloxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

2-(phenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a] isoquinolin-4-one

2-(2-methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

5. A compound of formula (Ia)



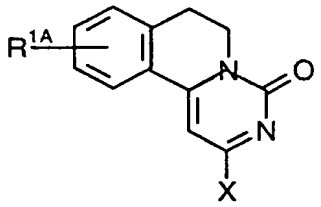
(Ia)

in which R^1 is hydrogen or up to three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl and hydroxy C_{1-6} alkyl,
R^2 is hydrogen or C_{1-6} alkyl, and
R^3 is C_{3-7} cycloalkyl, phenyl or phenyl C_{1-6} alkyl in which the cyclic moieties are optionally substituted by up to three substituents independently selected from halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylcarbonyl, hydroxy C_{1-6} alkyl and phenylcarbonyloxy C_{1-6} alkyl.

6. A compound selected from the group consisting of:
9,10-dimethoxy-2-(benzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(3-chlorobenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-methoxybenzoylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(3,5-dichlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(3-chlorophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-iodophenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-*iso*-propylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(N-methylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

9,10-dimethoxy-2-(cyclopentylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-Dimethoxy-2-(benzylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-acetylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-hydroxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
9,10-dimethoxy-2-(2-phenylcarbonyloxymethylphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one
2-(phenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a] isoquinolin-4-one
2-(2-methoxyphenylamino)-6,7-dihydro-4*H*-pyrimido[6,1-a]isoquinolin-4-one

7. A process for the preparation of a compound according to claim 5 or 6, which comprises reacting a compound of formula (II)



(II)

where R^{1A} is respectively R^1 as defined for formula (I) or a group convertible to R^1 with either

(a) a compound of formula $R^{3A}NR^{2A}H$, in which case X in formula (II) is a halogen (for compounds of formula (I) in which R is R^3), or

(b) a compound of formula $R^{3A}COY$ where Y is a halogen, in which case X in formula (II) is $NR^{2A}H$ (for compounds of formula (I) in which R is R^3CO),

where R^{2A} and R^{3A} are respectively R^2 and R^3 as defined for formula (I) or a group convertible to R^2 and R^3,

and where required converting an R^{1A}, R^{2A} or R^{3A} group to an R^1, R^2 or R^3 group, converting one R^1, R^2 or R^3 group to another R^1, R^2 or R^3 group, converting a salt product to the free base or another pharmaceutically acceptable salt, or converting a free base product to a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 98/02139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BASNI,LAL ET AL.: "TREQUINSIN,A POTENT NEW ANTIHYPERTENSIVE VASODILATATOR IN THE SERIES OF 2-(ARYLIMINO)-3-ALKYL-9,10-DIMETHOXY-3,4,6,7-TETRAHYDRO-2H-PYRIMIDO(6,1-A)ISOQUINOLINE-4-ONES." JOURNAL OF MEDICINAL CHEMISTRY., vol. 27, no. 11, 1984, pages 1470-1480, XP002076161 WASHINGTON US cited in the application see page 1473 - page 1480 ---	1,4-7
A	EP 0 124 893 A (HOFFMAN LA ROCHE) 14 November 1984 see the whole document --- -/--	1,4-7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 September 1998	21/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/EP 98/02139

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 370 379 A (HOECHST) 30 May 1990 see the whole document ---	1,4-6
A	US 5 114 944 A (CH.R.TAYLOR ET AL.) 19 May 1992 see column 15 - column 20 -----	1-3

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...ernational application No.
PCT/EP 98/02139

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1, 4
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1, 4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Inte ional Application No
PCT/EP 98/02139

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US 5114944 A	19-05-1992	NONE	